UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,883	01/10/2003	Yoshihiro Urade	2002-0487A	1364

513 7590 10/04/2005

WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
MONTANARI, DAVID A	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,883	URADE ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06/01/2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants arguments and amendments filed on June 1st, 2005 have been entered.

2. Claims 1, and 3-5 have been amended.

3. Rejection of claims 1-5 under 35 U.S.C. 103(a), has been withdrawn

4. Rejection of claims 1-5 under 35 U.S.C. 102(b), has been withdrawn.

5. Rejection of claims 1, and 3-5 under 35 U.S.C. 112, 2nd paragraph has been withdrawn.

6. Claims 1-5 are examined in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a human hematopoietic prostaglandin D2 (PGD2) synthase gene wherein said mouse expresses PGD2 in the lung, spleen, and liver at levels more than five times that of the endogenous PGD2 of the transgenic mouse and methods of using said mouse to test for *in vivo* activity for a candidate substance that reduces lung eosinophil levels after antigen insult, for a candidate substance that increases spontaneous locomotor activity after administration of lipopolysaccharide (LPS) at a dose of 20 mg/kg, and a candidate substance that reduces body-weight following a high-fat diet, does not reasonably provide enablement for any non-human animal comprising the human hematopoietic PGD2 synthase gene wherein said non-human animal over expresses PGD2 in the

lung, spleen, and liver at levels more than five times that of a wild-type animal and methods of using said non-human animal to test for *in vivo* activity for a candidate anti-allergy substance, a candidate sleep-lowering substance, and a candidate body-weight lower substance. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record in the office action dated 12/1/2004.

Claims 1-5 are drawn to non-human mammal overexpressing a human PGD2 synthase gene, and expressing human prostaglandin D2 synthase in the lung, spleen, and liver at levels more than five times that of a wild-type animal, wherein said non-human mammal is a mouse, a method for testing in vivo activity of a candidate anti-allergy substance using said non-human mammal or mouse, a method for testing in vivo activity of a candidate sleep-lowering substance using said non-human mammal or mouse, and a method of testing the in vivo activity of a candidate body weight-lowering substance using said non-human mammal or mouse.

Applicants arguments in amendment filed June 1st, 2005 have been fully considered but are not persuasive.

Applicants argue that the examiners characterization that only mice were known in the art at the time of filing to be genetically modified is incorrect. Applicants argue that there were many reports for making transgenic animals other than mice if one were to do a PubMed search with the term "transgenic animals" and cites Hammer et al. (transgenic rabbits, sheep and pigs), Knight et al. (transgenic rabbits), Vise et al. (transgenic pigs), and Mullins et al. (transgenic rats), as support. Applicants continue to argue that fertilized eggs or early embryos can be used for the generation of transgenic animals other than mouse ES-cells. Applicants continue to argue that at

the time of filing the skilled artisan upon reading the disclosure and given the knowledge in the art could make and use the full breadth of the claims without undue experimentation. This is not persuasive. A perusal of current art available to the skilled artisan with regard to the generation of transgenic animals would provide significant unpredictability for the skilled artisan to make and use claims 1-5 for their full breadth. Though the art cited by applicant does teach that it is possible to create other non-human transgenic animals other than mice, it does not teach the specific intricacies that would be required to make ALL non-human transgenic mammals overexpressing the human hematopoietic prostaglandin D2 synthase gene. For example, porpoises are non-human mammals, as well as the blue whale (*Balaenoptera musculus*), however the specification has provided no guidance that would enable the creation of a transgenic blue whale or porpoise over expressing the human hematopoietic prostaglandin D2 synthase gene. This is an issue, because when the claims are examined for enablement for their full-breadth, the creation of transgenic whales and porpoises would also be required since they are non-human mammals. With regard to current art, Ristevski et al., Houdebine, and Smith et al., teach the significant unpredictability and difficulty in generating transgenic animals. The art teaches that transgenic mouse lines are generated by microinjection of the linear DNA of interest into the nucleus of an oocyte or transfected into embryonic stem (ES) cells, which then randomly integrates into the genome (Ristevski, Molecular Biotechnology, Vol. 29, 2005, pg. 159 col. 1 parag. 2 lines 1-5). Currently only mouse ES cells have been established that result in a transgenic animal (Smith, 2002, J. of Biotechnology, Vol. 99, pg. 3 col. 1, parag. 4 lines 1-3). With regard to transgene integration the art teaches that the site of integration is uncontrolled and yet is critical due to the possibility of integration into a silent locus. Random integration may

occur, resulting in the insertional inactivation (insertional mutagenesis) of a gene at the site of integration, resulting in a loss of function that may be mistakenly attributed to over expression of the transgene (Ristevski, pg. 159 col. 1 parag. 2 lines 5-14). Further, insertional mutagenesis of a gene may not be immediately apparent if a recessive gene has been inactivated, as phenotypic abnormalities will not be evident until homozygous transgenic lines have been established (Ristevski, pg. 159 col. 1 parag. 2 lines 14-19). The site of integration may also result in altered tissue specificity, although the promoter used behaves differently at its normal chromosomal localization, with neighboring regulatory elements potentially influencing the transcriptional activity of the transgene (Ristevski, pg. 159 col. 1 parag. 3 lines 1-7). This is known as chromosomal position effects, where host sequences surrounding the site of transgene integration can alter the expected expression pattern, turning it ectopic or not detectable (Montoliu, 2002, Cloning and Stem Cells, Vol. 4, pg 39, col. 1). With regard to copy number the art teaches that controlling the transgene copy number (usually integration is a singular event with multiple copies integrated in tandem) is also problematic in the generation of transgenic animals (Ristevski, pg. 159 col. 1 parag. 3 lines 7-11). A high tandem copy number results in a gene silencing effect, and further, is undesirable if the effect of a gene dosage is being addressed, as multiple copies will not recapitulate relevant levels of expression (Ristevski, pg. 159 col. 1 parag. 3 lines 11-14 bridge col. 2 parag. 1). With regard to transgene expression, the art teaches bluntly that, "many transgenes work poorly" (Houdebine, 2002, J. of Biotechnology, Vol. 98, pg. 150, col. 1 parag. 4 line 1). Transgene expression is often very low or not specific of the promoter added in the gene construct, and are generally attributed to position effects in chromatin as discussed above (Houdebine, pg. 150, col. 1 parag. 4 lines 1-5). The art continues

to teach that a transgene is generally poorly expressed when it contains a cDNA rather than the corresponding genomic DNA sequence with its introns, has multiple copies integrated in the same site, and when a bacterial gene is used (Houdebine, pg. 150 col. 2 lines 4-9). Overexpression of a transgene of interest also has inherent problems. This is often the case when the overproduced protein shares only a part of the properties of an endogenous protein, which can result in inhibition of the endogenous protein, by the transgene of interest working in a transdominant negative manner (Houdebine, pg. 152, col. 2 parag. 4). The art continues that the generation of transgenic animals routinely involves one of two methods of exogenous DNA delivery to the recipient cells, retroviral infection or microinjection (Smith, pgs. 5-11). However, each method possesses significant unpredictability for the skilled artisan to implement. Retroviral vectors result in inconsistency and irreproducibility of transgene expression due to random integration with host DNA (Smith, pg. 6, col. 1 parag. 2), and instability due to the integrated retroviral DNA possessing the ability to spontaneously reactivate (Smith, pg. 6, col. 1 parag. 5). Microinjection of recipient cells with exogenous DNA presents the problem of mosaicism to the skilled artisan. The majority (≈ 85%) of pronuclear microinjection-derived transgenic founders are mosaics of transgenic and non-transgenic cells (Smith, pg. 7, col. 2 parag. 2 lines 1-4). This becomes problematic since transmission of the transgene is dependent upon the existence and extent of germline colonization by transgene-containing cells, so that when transmission does occur, the transgene is inherited in a mendelian fashion resulting in only a small portion of the transgene being passed onto offspring (Smith, pg. 7, col. 2 parag. 3, bridge pg. 8 col. 1 lines 1-8). Significant restraints also exist for the skilled artisan attempting microinjection of other animal species other than mouse. Cow, pig, and sheep eggs are optically

opaque, unlike mice, which makes microinjection of the targeted pronuclei extremely difficult (Smith, pg. 11 col. 2 parag. 1).

Given the unpredictability of creating any transgenic non-human mammal as taught above, the skilled artisan would required an undo amount of experimentation without a predictable degree of success to make and use the claimed invention.

Except for the conversion of the total lack of ennoblement to a scope of ennoblement rejection, a new ground of rejections has not been made.

Thus for reasons of record and above, the rejection is maintained.

No claims are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER